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| EXAMINER | |
|---|---|
| CHUNDURU, SURYAPRABHA | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/516,492 | KINZLER ET AL. | |
| | Examiner | Art Unit | |
| | Suryaprabha Chunduru | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,7,9-32,34 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,9-32,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## *DETAILED ACTION*

1. Applicants' response to the office action filed on October 23, 2007 has been considered and acknowledged.

### *Status of the Application*

2. Claims 1-4, 7, 9-32, 34-35 are pending. Claims 5-6, 8, 33 are cancelled. Claims 1, 19, 32 are amended. All arguments and amendment have been fully considered and deemed persuasive for the reasons that follow. The newly amended claim 1 recites 'human population' which was not present in the previously examined claims. Now the scope of the claims is changed. Accordingly new combination of prior art is applied as follows.

### *Objection to the specification*

3. The disclosure is objected to because of the following informalities:

(i) The drawings are labeled as Fig 1A, 1B and 1C and the brief description to the drawings on page 3-4 recite Fig. 1 to 3. No corresponding Figs 2 and 3 are found in the drawings and no description of the panels Fig 1A through 1C. Appropriate correction is required.

### *New Grounds of Rejections*

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)".

Here, the new limitation of "human population" in claim 1 appears to represent new matter. A careful review of the specification by the examiner revealed that 'human population' was not used. The specification recites 'allelic variation in human gene expression and the entire specification refers to analysis of human individuals for allelic variation and does not utilize any human population, instead a subset of human individuals were used for the analysis. Thus the limitation drawn to a human population lacks descriptive support in the specification.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A. Claims 1, 7, 9, 11-14, 16-18, 34, 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Egyed et al. (Forensic Science International, Vol. 113, pp. 25-27, 2000).

Egyed et al. teach a method of associating a genotype with a phenotype comprising (i) determining levels of expression of an allele of a gene in a first human population (Romanies population) comprising affected individuals, said affected individuals sharing a phenotype (see page 25, abstract, col. 2, paragraph 1 under section 2, page 26, col. 1, paragraphs 1-3);

(ii) determining levels of expression of the allele of the gene in a second human population comprising control samples (Hungarian Caucasian population) not sharing the phenotype, wherein said affected and control individuals are heterozygous for the gene, and wherein expression of the allele is determined independently of the expression of other alleles of the gene; comparing levels of expression of the allele in the first and second populations (see page 25, abstract, page 26, col. 1, paragraphs 1-3, col. 2, paragraph 1-2);

(iii) identifying the allele of the gene as having an association with the phenotype if its expression level differs in a statistically significant manner between the first and second populations (see page 26, col. 2, paragraphs 1-2, Fig. 1, page 27, col. 1, , line 1-9, paragraph 1).

With regard to claims 7, 9, Egyed et al. teach that the phenotype is a polymorphic phenotype and is not related to a known disease (see page 26, col. 2, paragraphs 1-2).

With regard to claims 11-14, Egyed et al. teach that the level of expression of the allele is heritable and determining the sequence variation which is associated with the allele in the first population and the variation is a single nucleotide polymorphism, which is an insertion (see page 26, col. 1, paragraphs 1-2, col. 2, paragraph 1).

With regard to claim 16, Egyed et al. teach that determining the sequence variation causes the level of expression of the allele to differ from level of expression of at least one other allele of the gene (see page 26, col. 2, paragraph 1, Fig. 1).

With regard to claim 17, Egyed et al. teach that the level of expression are determined and compared using fluorescent dye terminators (page 26, col. 1, paragraphs 1-2).

With regard to claim 18, Egyed et al. teach that the levels of expression are determined and compared using capillary electrophoresis ( page 26, col. 1, paragraph 1, col. 2, paragraph 1).

With regard to claims 34-35, Egyed et al. teach that a method comprising determining level of expression of an allele in a test individual (forensic blood sample from an individual), determining level of expression in a first and second population comprising controls (two Hungarian populations) and comparing level of expression of the allele in the test individual with the level of expression in the first and second populations, wherein a statistically significant difference in the level of expression between the test individual with the first and second populations identifies the association of that allele with the phenotype (see page 26, col. 2, paragraph 1). Accordingly Egyed et al. anticipates the instant claims.

B. Claims 1-2, 7, 11-13, 15-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Sieber et al. (PNAS, Vol. 99, No. 5, pp. 2954-2958, March 2002).

Sieber et al. teach a method of claim 1, associating a genotype with a phenotype comprising (i) determining levels of expression of an allele of a gene in a first human population comprising affected individuals, said affected individuals sharing a phenotype (colorectal polyposis) (see page 2954, col. 2, paragraph under patients and methods section, page 2955, col. 1, paragraphs 1-4);

(ii) determining levels of expression of the allele of the gene in a second human population comprising control samples not sharing the phenotype, wherein said affected and control individuals are heterozygous for the gene, and wherein expression of the allele is

determined independently of the expression of other alleles of the gene; comparing levels of expression of the allele in the first and second populations (see page 2954, col. 2, paragraph under patients and methods section, page 2955, col. 1, paragraphs 1-4, col. 2, paragraph 1);

(iii) identifying the allele of the gene as having an association with the phenotype if its expression level differs in a statistically significant manner between the first and second populations (see page 2955, col. 2, paragraph 1-2, page 2956, col. 2, paragraph 1).

With regard to claim 2, Sieber et al. teach that the phenotype is a disease (see page 2954, col. 1, paragraph 1, col. 2, paragraph under patients and methods section).

With regard to claim 7, Sieber et al. teach that the phenotype is a polymorphic phenotype (see page 2955, col. 2, paragraph 2).

With regard to claims 11-13, 15, Sieber et al. teach that the level of expression of the allele is heritable and determining the sequence variation which is associated with the allele in the first population and the variation is a single nucleotide polymorphism, which is a deletion (see page 2955, col. 2, line 1-17, paragraphs 1-2, page 2956, col. 1, line 1-9, col. 2, line 1-15).

With regard to claim 16, Sieber et al. teach that determining the sequence variation causes the level of expression of the allele to differ from level of expression of at least one other allele of the gene (see page 2956, col. 1, line 2-9,table 2).

With regard to claim 17, Sieber et al. teach that the level of expression are determined and compared using fluorescent dye terminators (page 2956, col. 2, line 9-15). Accordingly Sieber et al. anticipates the instant claims.

C. Claims 1-4, 7, 10-13, 16, 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Griseri et al. (European J Human Genetics, Vol. 8, pp. 721-724, 2000).

Griseri et al. teach a method of claim 1, associating a genotype with a phenotype comprising (i) determining levels of expression of an allele of a gene in a first human population (Italian HSCR (hirschsprung disease) patient population) comprising affected individuals, said affected individuals sharing a phenotype (see page 721, col. 2, paragraph 1, page 722, col. 1, paragraph 1);

(ii) determining levels of expression of the allele of the gene in a second human population comprising control samples (control Italian population) not sharing the phenotype, wherein said affected and control individuals are heterozygous for the gene, and wherein expression of the allele is determined independently of the expression of other alleles of the gene; comparing levels of expression of the allele in the first and second populations (see page 721, col. 2, paragraph 1, page 722, col. 1, paragraph 1, col. 2, paragraphs 1-3 under results section, table 1);

(iii) identifying the allele of the gene as having an association with the phenotype if its expression level differs in a statistically significant manner between the first and second populations (see page 722, col. 2, paragraphs 1-3 under results section);

With regard to claims 2-4, Griseri et al. teach that the phenotype is a birth defect (congenital defect) or herischsprung disease (see page 721, abstract, paragraph under introduction section).

With regard to claims 7, 10-13, Griseri et al. teach that the phenotype is a polymorphic phenotype and the expression is heritable change which includes single polymorphic nucleotide polymorphism and determining the haplotype associated with the allele (see page 721, col. 2, paragraph 1).

With regard to claim 16, 18, Griseri et al. teach that determining the sequence variation causes the level of expression of the allele to differ from level of expression of at least one other allele of the gene (see page 722, col. 2, paragraphs 1-3 under results section, page 723, paragraph 1 under discussion section Fig. 2) and analysis by capillary electrophoresis (see page 722, col. 1, paragraph 1 under functional assays. Accordingly Griseri et al. anticipates the instant claims.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griseri et al. (European J Human Genetics, Vol. 8, pp. 721-724, 2000) in view of Yoshikawa et al. (Anal Biochem., Vol. 256, pp. 82-91, 1998).

Griseri et al. teach a method of associating a genotype with a phenotype as discussed above in section 4C.

With regard to claims 19, 32, Griseri et al. also teach reverse transcribing mRNA from an individual and comparing the level of expression of an allele with a second allele (see page 722, col. 1, paragraph 2 under functional assays section).

With regard to claim 23-31, Griseri et al. teach the association of first and second allele in parent and offspring individuals and the trasmission of said alleles (see page 722, paragraphs 1-3 under results section).

However, Griseri et al. did not teach differential labeling of primers.

Yoshikawa et al. teach a method for differential display for detecting differentially expressed genes wherein the method comprises use of differentially labeled primers to detect differentially labeled cDNA fragments and comparison of differentially expressed cDNAs (see page 83, col. 1, paragraphs 1-2, col. 2, paragraphs 1-2, page 84, paragraph 1, page 85, Fig. 2, page 90, paragraph under discussion section).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of detecting allelic expression as disclosed by Griseri et al. with a step of differential labeling of primers as taught by Yoshikawa et al. for the purpose of developing a sensitive method for measuring allelic differences. One skilled in the art would be motivated to combine the method as disclosed by Griseri et al. with the method of Yoshikawa et al. because an ordinary artisan would have a reasonable expectation of success that the combination would result in a sensitive method for measuring expression levels because Yoshikawa et al. explicitly taught that the use of labeled primers enhanced the signal in PCR

amplification as compared to the signals using labeled nucleotides (see page 91, col. 1, line 1-26) and such modification of the method would be obvious over the cited prior art.

***Response to arguments***:

6. With regard to informalities to claims 32-33, Applicants' arguments and amendment are fully considered and the objection to the informalities is withdrawn herein in view of the amendment.

7. With regard to the rejection of claims 33-34 under 35 USC 112, second paragraph, Applicants' arguments and amendment are fully considered. With regard to claim 34, Applicants' arguments are found persuasive. Examiner notes that it was an inadvertent error in reciting claim 34 in the rejection, instead the rejection is directed to claim 32-33 based on the informalities noted. In view of the amendment and persuasive arguments, the rejection is withdrawn herein.

8. With regard to the rejection of claims 1-6, 9-16, 34-35 under 35 USC 102(b) as being anticipated by Lapidus et al. (US 5,928,870), Applicants' amendment and arguments are fully considered and found persuasive. The arguments regarding gene expression are unpersuasive. Applicants argue that gene expression is only dependent on mRNA and protein expression, which is found unpersuasive because the gene expression need not necessarily depend on mRNA and protein expression rather it is dependent on level of DNA expression. Further the instant specification on page 5 recite various DNA techniques to determine level of gene expression (see page 5, paragraph 15). However the rejection is withdrawn herein in view of the amendment.

9. With regard to the rejection of claims 1-15, 17, 19-20, 22-33 under 35 USC 102(b) as being anticipated by Lapidus et al. (US 6,146, 828), Applicants' amendment and arguments are fully considered and found persuasive. The rejection is withdrawn herein in view of the amendment.

10. With regard to the rejection of claims 18 and 21 under 35 USC 103(a) as being obvious over Lapidus et al. (US 6,146, 828) in view of Lapidus et al. (US 5,928,870), Applicants' amendment and arguments are fully considered and found persuasive. The rejection is withdrawn herein in view of the amendment and persuasive arguments.

***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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